# General

## Guideline Title

Eribulin for the treatment of locally advanced or metastatic breast cancer.

## Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Eribulin for the treatment of locally advanced or metastatic breast cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 67 p. (Technology appraisal guidance; no. 250).

## Guideline Status

This is the current release of the guideline.

# Recommendations

## Major Recommendations

- Eribulin is not recommended, within its licensed indication, for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease.
- People currently receiving eribulin, within its licensed indication, for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

- Locally advanced breast cancer
- Metastatic breast cancer

## Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

## Clinical Specialty

Internal Medicine

Obstetrics and Gynecology

Oncology

## Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

## Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of eribulin for the treatment of locally advanced or metastatic breast cancer

## Target Population

Patients with locally advanced or metastatic breast cancer

## Interventions and Practices Considered

Eribulin

## Major Outcomes Considered

- Clinical effectiveness
  - Overall survival
  - Progression free survival
  - Objective response rate
  - Duration of response
  - Clinical benefit rate
  - Adverse events
- Cost-effectiveness

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description and Appropriateness of Manufacturer's Search Strategy

The manufacturer describes the literature searches carried out up to August 2010. The ERG is confident that all major electronic databases were searched including the Cochrane Library (incorporating CENTRAL), Ovid Medline R, Medline In Process and Ovid EMBASE. Appropriate hand searching was conducted to identify any additional studies; this included clinicaltrials.gov, conference proceedings from the American Society of Clinical Oncology (ASCO) and the manufacturer's own clinical trial database. It is not stated whether the reference lists of previous trials or systematic reviews were also searched.

The manufacturer's submission (MS) provides a clear description of the searches carried out to identify primary relevant research. The comprehensive search strategy used drug names and no language restrictions were adopted. The ERG considers the search strategy to be appropriate. The ERG conducted its own searches up to 20th March 2011 (thus updating those presented in the MS) and is confident that no relevant studies have been missed by the manufacturer.

Inclusion/Exclusion Criteria

| | Inclusion | Exclusion |
|---|---|---|
| Population | Patients with locally advanced or metastatic breast cancer (LABC/MBC) | Patients with any other disease, including earlier stages of breast cancer |
| Intervention | Eribulin | Other interventions used for the treatment of LABC/MBC |
| Outcomes | Overall survival, progression-free survival, objective response rate, adverse event(s), health-related quality of life | Pharmacokinetic, pharmacodynamic outcomes (bioavailability, dose ranging) |
| Study design | Randomised controlled trials (RCTs), observational studies | Letters, reviews |

The ERG is satisfied with the clinical-effectiveness literature review process as described in the MS.

Economic Evaluation

Overview of Manufacturer's Cost-Effectiveness Review

The MS provides a description of the review of published cost-effectiveness evidence undertaken by the manufacturer. The databases searched and the search terms used appear to be reasonable and both inclusion and exclusion criteria are explicitly stated. The search by the manufacturer did not identify any relevant studies for inclusion in the review. Although there is no mention of searching within in-house databases for relevant studies, the ERG is confident that no relevant published studies are available for inclusion in the review.

Although the manufacturer did not identify any papers that had evaluated the cost-effectiveness of eribulin as a third-line treatment for metastatic breast cancer (MBC), the MS included data extraction tables and quality assessment reviews of nine economic evaluations that were considered relevant to inform the structure, assumptions and model inputs for the cost-effectiveness analysis of eribulin for the treatment of women with locally advanced breast cancer (LABC)/MBC in the UK.

## Number of Source Documents

Clinical Effectiveness

One randomised controlled trial (RCT) and 3 non-RCTs were included in the review.

Cost-effectiveness

- No relevant studies for inclusion in the review were identified.
- Nine economic evaluations were considered relevant to inform the structure, assumptions and model inputs for the cost-effectiveness analysis.
- The manufacturer submitted an economic model.

## Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

## Rating Scheme for the Strength of the Evidence

Not applicable

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field.)

Clinical Effectiveness

Description and Critique of Manufacturers Approach to Validity Assessment

A single phase III randomised controlled trial (RCT) (EMBRACE) forms the basis of the majority of the clinical and cost-effectiveness evidence in the manufacturer's submission (MS). Evidence from three phase II single-arm studies is presented to supplement evidence from the EMBRACE trial.

*Trial Conduct*

The EMBRACE trial is a large, international, multi-centre, open-label RCT. The manufacturer has provided a quality assessment of the trial in the MS; this has been critiqued by the ERG and appears in Appendix 1 of the ERG report (see the "Availability of Companion Documents" field). The ERG considers the EMBRACE trial to be a well-designed trial.

Randomisation to eribulin or treatment of physician's choice (TPC) was conducted in a 2:1 ratio to receive either eribulin or TPC. In addition, a TPC treatment was identified (via clinician/patient decision) for each patient prior to randomisation; the choice was confirmed by the investigator using the interactive voice response system. The purpose of this was to ensure that each TPC treatment was independently randomised against eribulin to support the conduct and results of subgroup analyses. The ERG considers the method of randomisation used in the EMBRACE trial to be robust.

The ERG has concerns regarding the number of patients in EMBRACE trial who were not assessed regularly after baseline. The trial protocol specified that patients were to be followed up every 8 weeks; however, analysis of the clinical data shows that at least 50 patients missed at least one or more scheduled scans. This suggests that the conduct of the trial may not have matched the high standard of the trial design in some aspects.

It is important that the inclusion and exclusion criteria remain unchanged during study recruitment. In response to the ERG's request for clarification, the manufacturer stated that 46 (9.1%) patients in eribulin arm and 32 (13%) patients in the TPC arm violated the EMBRACE trial protocol with regard to the trial eligibility criteria. The most frequently observed violations related to the patient not being refractory to the most recent chemotherapy (CTX) (16/3.1% in the eribulin arm and 11/4.3% in the TPC arm), followed by patients having received more than five prior CTX regimens (15/3.0% patients in the eribulin arm and 9/3.5% patients in the TPC arm) and the patient having received only one regimen for locally recurrent or metastatic disease (7/1.4% in the eribulin arm and none in the TPC arm).

Given the large number of protocol violations of major inclusion and exclusion criteria, the ERG considers that the approach to study monitoring was not adequate with respect to ensuring that patients met eligibility criteria. However, the protocol violations were relatively evenly distributed across the two treatment arms. It is therefore unlikely that these protocol violations had any impact on the overall study results, as evidenced by the results of the per protocol analysis.

*Blinding*

In the EMBRACE trial, patients and investigators were not blinded to treatment allocation. From a pragmatic point of view, this is reasonable given that there were a number of different comparator treatments administered in the trial and each comparator has a different dosing regimen and method of administration. Furthermore, the primary outcome of the EMBRACE trial was overall survival (OS) and the assessment of OS is not dependent on subjective assessment. For the trial outcomes dependent on subjective assessment, blinded review was conducted.

Describe and Critique the Statistical Approach Used

The ERG considered the statistical approaches employed in the EMBRACE trial to be generally appropriate. The Statistical Analysis Plan (SAP) for the EMBRACE trial was rightly prepared before database lock and intention-to-treat (ITT) analysis was conducted. However, the ERG notes that changes to the planned analyses were made to incorporate *post-hoc* analyses and subgroups after database lock and thus a number of *post-hoc* and subgroup analyses are also reported. The main change to the analysis plan that may impact on selection bias involved splitting the TPC treatment arm into seven groups (capecitabine, vinorelbine, gemcitabine, taxanes, anthracyclines, hormonal therapy and other drugs) without appropriate adjustment for multiple testing, thus increasing the risk of chance findings. The ERG considers that the results from the *post-hoc* analyses of eribulin versus individual TPC should be interpreted with caution since these analyses were defined after database lock and the large number of comparisons performed increase the risk of chance findings.

The EMBRACE trial was the main source for the clinical evaluation as it was the only study directly comparing eribulin and TPC. Therefore, no meta-analysis or indirect comparison was performed by the manufacturer.

See Section 4 of the ERG report (see the "Availability of Companion Documents" field) for additional information.

Economic Evaluation

Description of Manufacturer's Economic Model

The manufacturer constructed a semi-Markov state transition model in Microsoft Excel to model the lifetime clinical and economic outcomes for a hypothetical cohort of patients with locally advanced of metastatic breast cancer (LABC/MBC). The ERG notes that a trial duration time horizon is adopted in the model. This means that at the end of the duration of the trial (2.89 years), all patients that are alive are transitioned into a 'terminal' state and no extrapolation of trial outcomes is undertaken. The model assumes an average body surface area (BSA) of 1.74$m^2$.

The model consists of three main health states: treated, progressive and dead. All patients in the model were initially assigned to the 'treated' health state which comprises both stable and responsive patients. These patients matched those recruited into the EMBRACE trial and were therefore eligible for treatment with eribulin or the treatment options within TPC.

Parameters and values used by the manufacturer in the economic model are described in Table 21 of the ERG report (see the "Availability of Companion Documents" field).

Model Validation

The methodological approach to economic modelling adopted by the manufacturer was validated by a Professor of Health Economics based at a UK university. Validation of data inputs was carried out in consultation with UK clinicians and commissioners of oncology treatment services.

The manufacturer provided details of the model validation checklist used. The economic model was checked for functionality, clarity, accuracy, consistency, validity and platform along the project lifecycle.

See Section 5 of the ERG report (see the "Availability of Companion Documents" field) for additional information.

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

## Rating Scheme for the Strength of the Recommendations

Not applicable

## Cost Analysis

The manufacturer developed a semi-Markov state transition model that compared eribulin monotherapy with treatment of physician's choice (TPC) as well as individual chemotherapy agents (capecitabine, gemcitabine and vinorelbine). Data from patients in region 1 of the EMBRACE trial were used in the manufacturer's base-case analyses because the manufacturer considered this population to be most relevant to clinical practice in England and Wales. The manufacturer conducted a sensitivity analysis using data from the overall intention-to-treat (ITT) population. The Department of Health has approved a patient access scheme for eribulin and these discounted costs were incorporated in the manufacturer's analysis.

The manufacturer presented four scenarios as the base-case analysis based on region 1 data. These were eribulin versus TPC as reported in the EMBRACE trial, and eribulin versus the three individual drugs outlined in the National Institute for Health and Clinical Excellence (NICE) scope:

capecitabine, vinorelbine and gemcitabine. The base-case results for each of the comparisons indicated incremental costs for eribulin of £5586, £5177, £4041 and £12,779 compared with TPC, gemcitabine, vinorelbine and capecitabine respectively and incremental quality-adjusted life years (QALYs) of 0.1213, 0.1904, 0.1136 and 0.2683 respectively. This resulted in incremental cost-effectiveness ratios (ICERs) for eribulin of £46,050 per QALY gained versus TPC, £27,183 versus gemcitabine, £35,602 versus vinorelbine and £47,631 versus capecitabine.

The Evidence Review Group (ERG) commented that the manufacturer's economic model was generally well constructed and in line with the scope issued by NICE. The ERG also highlighted several issues around the identification, measurement and valuation of costs and consequences.

The ERG also noted that the cost of administration of chemotherapy estimated in the manufacturer's submission may not be accurate for several reasons: unit costs of administration relating to the National Health Service (NHS) Reference Cost Schedule 08/09 were used, rather than the most recent figures from the NHS Reference Cost Schedule 09/10; all chemotherapy administration was allocated to an outpatient department, but clinical advice to the ERG indicated that such therapy would normally be administered in a designated chemotherapy day-case unit; the manufacturer had not incorporated the different healthcare resource group costs appropriate to the first administration of a course of therapy (using the 'subsequent cycles' costs instead). Adjusting for these discrepancies resulted in higher costs of administration in nearly all cycles of both arms of the model.

Summary of Appraisal Committee's Key Conclusions

The Committee agreed that it was more appropriate to use the ERG's exploratory analysis that projected survival trends to the end of life in line with the lifetime time horizon recommended in the NICE methods guide.

The Committee agreed that costs of administration should take into account chemotherapy day-case unit costs rather than outpatient department costs and that healthcare resource group costs appropriate to the first administration of a course of therapy should be included alongside costs for subsequent cycles. The Committee also supported the ERG's use of the most recent NHS Reference Costs.

The Committee agreed that the ERG's exploratory analyses of the manufacturer's model for the overall ITT population, which included the ERG's projection of overall survival and re-estimation of costs, resulted in a more plausible estimate for the cost-effectiveness of eribulin compared with TPC (that is £68,600 per QALY gained), than the manufacturer's estimate. However, the Committee considered that this figure was likely to underestimate the true cost per QALY gained of eribulin relative to TPC because it did not incorporate the full toxicity profile of eribulin, including the disutility associated with alopecia. In addition, significant uncertainties remained about health-related quality of life associated with eribulin. Furthermore, the Committee was aware that some of its concerns about costs were not accounted for in the ERG's exploratory analyses, including less frequent administration of vinorelbine, the use of generic prices to estimate the price of the comparators and the national discounts available to the NHS for vinorelbine.

The Committee considered that it had not been presented with a most plausible estimate of the ICER for eribulin versus vinorelbine in the prior capecitabine-treated subgroup because of the lack of a robust survival advantage in this setting. The Committee concluded that eribulin could not be considered a cost-effective use of resources for NHS use.

See Sections 3 and 4 of the original guideline document for details of the economic analyses provided by the manufacturers, the ERG comments, and the Appraisal Committee considerations.

## Method of Guideline Validation

External Peer Review

## Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of eribulin and a review of this submission by the Evidence Review Group (ERG). For clinical effectiveness, one randomised controlled trial (EMBRACE) was the main source of evidence. For cost-effectiveness, nine economic evaluations and the manufacturer's economic model were considered.

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Appropriate recommendations regarding the use of locally advanced or metastatic breast cancer

## Potential Harms

The most common adverse effects of eribulin are fatigue, alopecia, peripheral neuropathy, nausea, neutropenia, leukopenia and anaemia.

For full details of side effects and contraindications, see the summary of product characteristics.

# Contraindications

## Contraindications

For full details of side effects and contraindications, see the summary of product characteristics.

# Qualifying Statements

## Qualifying Statements

- This guidance represents the views of the National Institute for Health and Clinical Excellence (NICE), and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

# Implementation of the Guideline

## Description of Implementation Strategy

- The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the National Health

Service (NHS) in England and Wales on implementing National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

- NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on the NICE Web site (http://guidance.nice.org.uk/TA250 ).
  - A costing statement explaining the resource impact of this guidance

### Implementation Tools

Audit Criteria/Indicators

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

End of Life Care

Living with Illness

### IOM Domain

Effectiveness

Patient-centeredness

## Identifying Information and Availability

### Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Eribulin for the treatment of locally advanced or metastatic breast cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 67 p. (Technology appraisal guidance; no. 250).

### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2012 Apr

## Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

## Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

## Guideline Committee

Appraisal Committee

## Composition of Group That Authored the Guideline

*Committee Members*: Professor Darren Ashcroft, Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester; Dr Matthew Bradley, Value Demonstration Director, AstraZeneca; Professor Usha Chakravarthy, Professor of Ophthalmology and Vision Sciences, The Queen's University of Belfast; Professor Peter Clark (*Chair*), Consultant Medical Oncologist, Clatterbridge Centre for Oncology; Dr Ian Davidson, Lecturer in Rehabilitation, University of Manchester; Professor Simon Dixon, Senior Lecturer in Health Economics, University of Sheffield; Dr Martin Duerden, Assistant Medical Director, Betsi Cadwaladr University Health Board; Dr Alexander Dyker, Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle; Gillian Ells, Prescribing Advisor, NHS Sussex Downs and Weald; Paula Ghaneh, Senior Lecturer and Honorary Consultant, University of Liverpool; Niru Goenka, Consultant Physician, Countess of Chester NHS Foundation Trust; Dr Susan Griffin, Research Fellow, Centre for Health Economics, University of York; Professor Carol Haigh, Professor in Nursing, Manchester Metropolitan University; Alison Hawdale, Lay member; Professor John Hutton, Professor of Health Economics, University of York; Professor Peter Jones, Emeritus Professor of Statistics, Keele University; Dr Vincent Kirkbride, Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield; Dr Rachel Lewis, Advanced Nurse Practitioner, Manchester Business School; Dr Anne McCune, Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust; Professor Jonathan Michaels (*Vice Chair*), Professor of Clinical Decision Science, University of Sheffield; Professor Femi Oyebode, Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health; Dr John Radford, Director of Public Health, Rotherham Primary Care Trust; Dr Phillip Rutledge, GP and Consultant in Medicines Management, NHS Lothian; Dr Brian Shine, Consultant Chemical Pathologist, John Radcliffe Hospital; Dr Murray D Smith, Associate Professor in Social Research in Medicines and Health, University of Nottingham; Paddy Storrie, Lay member; Mike Wallace, Health Economics and Reimbursement Director, Johnson & Johnson Medical Ltd; Dr Lok Yap, Consultant in Acute Medicine and Clinical Pharmacology, Whittington Hospitals NHS Trust

## Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

## Guideline Status

This is the current release of the guideline.

## Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

## Availability of Companion Documents

The following are available:

- Eribulin for the treatment of locally advanced or metastatic breast cancer. Costing statement. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 4 p. (Technology appraisal guidance; no. 250). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Eribulin for the treatment of locally advanced or metastatic breast cancer. Evidence Review Group report. Liverpool (UK): Liverpool Reviews and Implementation Group, University of Liverpool; 2011 May 24. 89 p. Electronic copies: Available in PDF from the NICE Web site .

## Patient Resources

The following is available:

- Eribulin for locally advanced or metastatic breast cancer. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 5 p. (Technology appraisal guidance; no. 250). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

## NGC Status

This NGC summary was completed by ECRI Institute on July 18, 2012.

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